The Cost Effectiveness of Inhaled Steroid Withdrawal in Outpatients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: In Chronic Obstructive Pulmonary Disease (COPD), evidence with regard to effectiveness and safety of inhaled corticosteroids (ICS) is inconclusive. This study determines the cost effectiveness of withdrawing the ICS Fluticasone propionate (FP) in outpatients with COPD.

Methods: The cost-effectiveness analysis was based on a randomized, placebo controlled FP-withdrawal study. After a four-month run-in period on FP, patients were randomly assigned to continue FP 500 µg twice daily or to receive placebo for 6 months. A decision analytic model evaluated the 6-month incremental cost-effectiveness of the ICS versus ICS-withdrawal strategy. One-way sensitivity analyses and a Monte Carlo simulation were performed to evaluate the robustness of the findings.

Results: The average patient with COPD in the FP group generated € 511 in direct medical cost, including € 238 for FP. The cost of the placebo strategy was € 456. The higher direct drug cost of € 212 per patient in the six months of follow-up of the FP strategy compared to the placebo group was partially offset by a € 157 lower exacerbation and hospitalisation cost. The 6-month incremental cost-effectiveness of the FP strategy compared to placebo was € 110 per exacerbation prevented and € 1,286 per hospitalisation prevented.

Discussion: Over six-months withdrawing FP in a pre-selected trial population of COPD patients led to absolute cost-savings but with a higher exacerbation and hospitalisation rate.
INTRODUCTION
Chronic Obstructive Pulmonary Disease (COPD) is a common disease that affects up to 24 million people in the USA and leads to substantial disability and death. Patients with COPD have about 3 exacerbations of their disease per year, many of which result in unscheduled visits to a physician or emergency department and to hospitalisation. Clinicians regularly prescribe long-term inhaled corticosteroids (ICS) for the management of COPD, as ICS are effective in controlling inflammation in asthma, and both asthma and COPD result from chronic inflammation. However, the inflammatory pattern of COPD is different from that of asthma, and evidence with regard to the effectiveness and safety of ICS in COPD is contradictory. Recent meta-analyses also show conflicting results with regard to the ability of inhaled steroids in arresting the long-term decline in FEV1 in COPD and its effects on symptoms and numbers of exacerbations. Tradeoffs between potential clinical benefits and harms remain unclear. However, the GOLD COPD guidelines recommend that in patients with a FEV1 percent predicted of less than 50% and frequent exacerbations ICS should be prescribed.

Only four studies have investigated the effect of withdrawal of ICS in COPD: 1) an observational, non randomized, study as part of the run-in phase of the ISOLDE study, 2) a small, underpowered crossover study with a short follow-up and no wash-out period, 3) our own study, the COPE study, and recently, the COSMIC study. In the run-in phase of the ISOLDE study, ICS were withheld from patients already using these medications. In the first 7 weeks post withdrawal, 38% of patients previously treated with ICS experienced an exacerbation compared to 6% of those who had not previously received ICS. Similarly, in the COPE study the majority of exacerbations also occurred in the first seven weeks. The crossover study by O’Brien et al. demonstrated that withdrawal of ICS in elderly patients with COPD led to deterioration in ventilatory function and increased exercise-induced dyspnea and showed a trend towards an increased frequency of exacerbations. However, results of this small cross-over study should be viewed with caution as only 15 of the 24 patients completed the study, and follow-up was only 12 weeks. Clinical results of the COPE study are published in detail elsewhere. In brief, the following results were reported. After 4 months of treatment with FP (1000 mg/day), 244 patients were randomized to either continue FP or to receive placebo for 6 months: In the placebo-group, 26 patients (21.5%) experienced rapid recurrent exacerbations and were subsequently unblinded and prescribed open FP compared to 6 patients (4.9%) in the FP-group (Relative Risk = 4.4; 95% CI 1.9-10.3). With regard to the effect of ICS withdrawal on exacerbations, the COSMIC study showed a doubling of the incidence rate of mild exacerbations, but not moderate to severe exacerbations, in the year after withdrawing ICS in COPD patients also using salmeterol.

The objective of the current economic evaluation was to assess the cost effectiveness of withdrawing the ICS Fluticasone propionate (FP) 500 µg twice daily in outpatients with COPD based on the six months of follow-up in the COPE study. We utilized decision modeling techniques to assess differences in total costs as well as cost per exacerbation and hospitalisation prevented over the six month trial timeframe. Modeling allowed us to explore variation in parameters to enhance generalizability.

PATIENTS AND METHODS
Clinical data
The COPE study was a randomized, double blind, parallel-group single center study with a 4 months run-in period, and 6 months active treatment or placebo, with follow-up visits at 3 and 6 months. The inclusion criteria and design have been described previously and is summarized briefly below. In the run-in phase, all patients were prescribed FP via Diskus
500 µg twice daily to optimize lung function. After the four months, eligible patients were randomly assigned to continue FP 500 µg twice daily or to receive placebo for 6 months. If patients experienced any worsening of their respiratory symptoms, they were invited to attend the hospital within 12 hours for spirometry measurements and consultation by one of the study physicians who subsequently decided either to continue the trial or to prescribe FP 500 µg twice daily unblinded. The latter was allowed according to the benefit of the doubt principle in case patients experienced rapid recurrent exacerbations. This was defined as either twice an objective increase in respiratory symptoms within a 3-month period, defined as more than 20% or 300 ml decrease in FEV1, compared with stable lung function at randomisation, or three times a subjective increase of respiratory symptoms in a 3-month period as experienced by the patient regardless of the above-mentioned criteria. For patients who were already on FP, therapy did therefore not change; only the blinding was gone.

Economic evaluation using a decision analytic model

A decision analytic model with a time perspective of six months was developed to evaluate the short-term (incremental) cost-effectiveness of the ICS versus withdrawal strategy. Figure 1 depicts the decision analytic model. Table 1 presents the base-case probabilities with the associated 95% Confidence Intervals (95% CI) for each step in the model. All data come from the COPE study.

### Table 1. Base-case values of probabilities of exacerbations and hospitalisations

| Probability of rapid recurrent exacerbations | FP* (0.049 (.023 - .102)) | Placebo (0.215 (.151 - .296)) |
| Probability of further exacerbations when returned to open FP | .833 (.436 - .970) | .385 (.224 - .575) |
| Probability of at least one hospital admission in patients that continue to experience exacerbations following use of open FP | .400 (.118 - .769) | .300 (.108 - .603) |
| Probability of at least one hospital admission during the six month trial period in patients that are free of exacerbations following use of open FP | .000 (.000 - .793) | .063 (.011 - .283) |
| Probability of at least one exacerbation in patients not experiencing recurrent exacerbations | .445 (.358 - .535) | .453 (.356 - .553) |
| Probability of at least one hospitalisation in patients not experiencing recurrent exacerbations | .135 (.067 - .253) | .116 (.051 - .245) |

* Fluticasone Propionate

Base-case cost effectiveness analyses were performed according to the U.S. panel on CEA guidelines. However, indirect costs, such as lost productivity during usual daily activities were excluded from the base-case analyses, thus assuming the health care payer’s perspective. The cost effectiveness ratio was calculated as cost per exacerbation prevented and cost per hospitalisation prevented, respectively. One-way sensitivity analyses were performed to evaluate the relative impact of the various parameters in the decision analytic model. Cost components with the exception of hospital costs were varied over a range of 50 – 150% of the actual cost. The probabilities of experiencing exacerbations, hospitalisations and the costs associated with hospital admissions were varied between the lower and upper 95% Confidence Interval (CI) as derived from the COPE trial data. A Monte Carlo simulation with 1000 iterations was done to explore the variation in the total costs as well as cost per exacerbation and hospitalisation prevented when cost parameters and probabilities were
varied simultaneously over their ranges and associated 95% CI. For the cost of exacerbations and FP triangular distributions were used. The reason for varying the cost of FP in the model was to facilitate generalisation to situations where inhaled corticosteroids are cheaper or more expensive. For the cost of a hospitalisation a Normal distribution was used, while a logistic-normal distribution was used for all probabilities.\textsuperscript{16}

**Resources and Cost**

Health care resource use was prospectively recorded during the COPE study by active follow-up of the patients' records, both in-patient and outpatient, with regard to hospitalisations, emergency room visits, scheduled and emergency outpatient visits. At each visit patients were questioned about possible adverse events and health care contacts. We also contacted all the patients’ general practitioners to enquire about treated exacerbations of COPD at the end of the six month follow-up. Pharmacists reported all drugs used during the study period. Current Dutch guidelines on good pharmaco-economic practice specify that costs estimated at a national average level should be used as much as possible.\textsuperscript{17} Resource use, including the salary of the pulmonary physicians and lung function technicians was multiplied with 2002 unit prices.\textsuperscript{18,19} Medication cost for FP, prednisolone and amoxicillin/clavulanate were based on market prices and included a €6 dispensing fee added for each 6-month period. During the trial, 21.5\% of patients in the placebo group experienced recurrent exacerbations and they resumed open FP for the remainder of the trial. On average they used FP for 50\% (91 days) of the entire trial period of 6 months.

Where applicable, Dutch guilders were converted into Euros (1 Euro (€) = NLG 2.20). For conversion to U.S. dollars, costs in euros should be multiplied by a factor of 0.934, based on the 2002 Purchasing Power Parities as issued by the organisation for Economic Co-operation and Development (www.oecd.org). Due to the short-time perspective, costs and effects were not discounted for time preferences.

**RESULTS**

**Base-case Cost Effectiveness Analysis of the trial**

The 6-month cost and effect data are presented in Table 2. The average patient with COPD in the FP group generated €511 in direct medical cost, including €238 for FP. The cost of the placebo strategy was €456. The higher direct drug cost of €212 per patient in the six months of follow-up of the FP strategy compared to the placebo group was partially offset by a €157 lower exacerbation and hospitalisation cost.
Table 2. The six month cost (€) and effects of withdrawal of Fluticasone Propionate 500 µg b.i.d. versus placebo in outpatients with COPD, using 2002 cost prices

<table>
<thead>
<tr>
<th></th>
<th>FP* strategy</th>
<th>Placebo strategy</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost per patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone Propionate 500 µg b.i.d. †</td>
<td>238</td>
<td>26</td>
<td>212</td>
</tr>
<tr>
<td>Exacerbation cost ‡</td>
<td>59</td>
<td>93</td>
<td>-34</td>
</tr>
<tr>
<td>Hospitalisation §</td>
<td>214</td>
<td>337</td>
<td>-123</td>
</tr>
<tr>
<td>Total direct medical cost</td>
<td>511</td>
<td>456</td>
<td>55</td>
</tr>
<tr>
<td><strong>Effect per patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of exacerbations</td>
<td>0.87</td>
<td>1.37</td>
<td>-0.50</td>
</tr>
<tr>
<td>Number of hospitalisations</td>
<td>0.073</td>
<td>0.116</td>
<td>-0.043</td>
</tr>
</tbody>
</table>

* Fluticasone Propionate
† Includes €6 pharmacy cost/prescription
‡ Includes salary cost of pulmonary physician and lung function assistant, as well as cost for courses of oral steroids and antibiotics, including €6 pharmacy cost/prescription
§ Average of 10.5 hospital days

In the base-case cost effectiveness analysis, the 6-month incremental cost-effectiveness of the FP strategy compared to placebo was €110 per exacerbation prevented and €1,286 per hospitalisation prevented. The corresponding Number Needed to Treat (NNT) to prevent one exacerbation is 2 while the NNT to prevent one hospitalisation is 24.

Sensitivity analysis of the decision analytic model
The results from the cost effectiveness analysis with regard to cost per exacerbation and hospitalisation prevented were sensitive to change in various parameters (Figure 2). The Tornado diagram shows how the main outcome parameter (cost per exacerbation prevented) varies when the various inputs in the decision tree (probabilities, RR of recurrent exacerbations, and costs) are varied according to their distributions (Normal and logistic-normal distributions with their associated 95% CI for hospital costs and probabilities mentioned in table 1, as well as the RR, respectively; triangular distributions for the cost of exacerbations and FP).

When the RR of recurrent exacerbations following FP-withdrawal (RR observed in the COPE study = 4.4) decreases to the lower limit of the 95% CI (RR = 1.9), the FP strategy exceeds a cost of €1000 per exacerbation prevented. At a RR of 5.4, both alternatives are equally costly. The same is true if the cost of FP is reduced to 75% of the base-case cost at €177 per six months. The results are also sensitive to the probability of a hospitalisation in those who develop recurrent exacerbations following FP-withdrawal but remain without exacerbations following use of open FP. At the upper limit of the 95% CI, with a probability of a hospitalisation of 28%, the FP strategy would save €571 per exacerbation prevented. Furthermore, the results are sensitive, but to a lesser degree, to the probability of a hospitalisation in those who develop recurrent exacerbations following FP-withdrawal and continue to have subsequent exacerbations following use of open FP (range of cost per exacerbation prevented from €264 to a saving of €134) and in those who only have an occasional exacerbation following FP-withdrawal (range of cost per exacerbation prevented from €245 to a saving of €157). Finally, the results are sensitive to the probability of a
hospitalisation in those who remain on FP and only have an occasional exacerbations (range of cost per exacerbation prevented from € 402 to a saving of € 57).

A Monte Carlo simulation with 1000 iterations reached convergence and Figure 3 shows the results of the simulations in cost per exacerbation prevented. The median cost per exacerbation prevented was € 127 (interquartile range -€ 52 to € 331). Figure 4 shows the cost per hospitalisation prevented. The median cost per hospitalisation prevented was € 122 (interquartile range -€ 1411 to € 3069).

DISCUSSION
In the base-case cost effectiveness analysis, the 6-month incremental cost-effectiveness of the FP strategy compared to placebo was € 110 per exacerbation prevented and € 1.286 per hospitalisation prevented. However, sensitivity analyses showed that the short-term results are sensitive to the risk of recurrent exacerbations when withdrawing FP. The COPE study showed that only a minority of patients will develop these recurrent exacerbations, following ICS withdrawal. The recently published COSMIC study showed a doubling of the incidence rate of mild exacerbations, but not moderate to severe exacerbations, in the year after withdrawing ICS in COPD patients also using salmeterol. Both studies do not provide evidence of a great danger of at least trying the withdrawal strategy. Also, these two studies are studies of exacerbations when ICS are stopped and do not provide evidence about whether the incidence rate of exacerbations will be reduced when ICS are started.

When the risk of exacerbations with the withdrawal of FP becomes relatively low, the FP strategy becomes very expensive. Given the sensitivity of the cost-effectiveness ratio to the risk of recurrent exacerbations when withdrawing FP, it is important to identify patients with COPD in whom withdrawing FP is likely to be safe or not. The GOLD COPD guidelines recommend that in patients with a FEV1 percent predicted of less than 50% and frequent exacerbations ICS be prescribed. Analysis of the subgroup of patients with a FEV1 <50% predicted in the COPD ICS-withdrawal study suggested that the difference in time to first exacerbation between groups was driven by this subset.

The results were also sensitive to the cost of FP. The sensitivity analysis of the trial results also shows that the FP-strategy becomes very expensive if the cost of FP per patient is doubled. This can be a result of doubling the dose of FP. However, this is not very realistic, because the patients in the study already received 1000 µg per day, which is considered to be the maximum dose patients should be prescribed as maintenance therapy. It can also be doubled when FP is twice as expensive, which could be the case in other countries. If the cost of FP would be reduced to below 75%, the FP strategy becomes dominant. If this reduction in monthly cost is achieved with the same dosage of 1000 µg per day, this holds true.

The unfavorable effects of withdrawing FP manifest themselves at an early stage. Among patients that were returned on open FP, the average time it took to develop two objective exacerbations was exactly 3 months, from the moment FP was withdrawn. When patients are subsequently returned on FP, it can be argued that they will have a similar future risk of adverse events as patients who remained on FP. A long-term study of withdrawing ICS in all COPD patients and only resuming ICS in those with rapid recurrent exacerbations might shed light on this matter.

In summary, withdrawing FP in a pre-selected trial population of COPD patients led to absolute cost-savings but with a higher exacerbation and hospitalisation rate. However, in the long run, withdrawing inhaled steroids in patients already on long-term ICS therapy, and close follow-up to see if they deteriorate in the first few months, might be an appropriate strategy. Those who have rapid recurrent exacerbations following withdrawal should be returned on inhaled steroids. Pre-screening patients (e.g. those without asthmatic features) is highly recommended, both to prevent unnecessary harm to patients, as to prevent an unnecessary high workload for the physician.
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COMPETING INTEREST STATEMENT
None of the authors have competing interests with regard to this manuscript.

The study was approved by the Medical Ethical Committee of Medisch Spectrum Twente, Enschede, The Netherlands. All patients in the COPE study gave informed consent.

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Legends of figures
1. Decision analytic model with probabilities of exacerbations and hospitalisations for the inhaled corticosteroid strategy and the placebo strategy.
2. Tornado diagram for cost per exacerbation prevented. A positive change from base value favors the placebo strategy.
3. Results of a Monte Carlo simulation on cost per exacerbation prevented. A positive €-amount favors the placebo strategy. A positive difference in nr of exacerbations favors the FP-strategy.
4. Results of a Monte Carlo simulation on cost per hospitalisation prevented. A positive €-amount favors the placebo strategy. A positive difference in nr of exacerbations favors the FP-strategy.

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Figure 2

% Change from Base Value

-700% -500% -300% -100% 100% 300% 500% 700% 900%

- RR of recurrent exacerbations
  Prob (hospitalization | no FP, A & B)
  Prob (hospitalization | FP, D)
  Cost of FP
  Prob (hospitalization | no FP, D)
  Prob (hospitalization | no FP, A & C)
  Prob (exacerbation | FP, D)
  Prob (exacerbation | no FP, D)
  Prob (exacerbation | no FP, A)
  Prob (hospitalization | FP, A & C)
  Cost of a hospitalization
  Prob (exacerbation | FP, A)
  Cost of an exacerbation
  Prob (hospitalization | FP, A & B)

A: recurrent exacerbations leading to use of open FP
B: no further exacerbations following use of open FP
C: further exacerbations following use of open FP
D: occasional exacerbation, not leading to use of open FP
Figure 3
The cost effectiveness of inhaled steroid withdrawal in outpatients with chronic obstructive pulmonary disease

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